

Safety profile of end-stage heart failure patients implanted with left ventricular assist devices. Krakow two-year observational all-comers study on left ventricular assist device recipients

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INTRODUCTION

Heart transplantation (HTx) is an established line of treatment for advanced heart failure (HF), but with a shortage of donor organs its impact is limited. Therefore, the demand for efficacious and safe mechanical left ventricular assist devices (LVADs) is increasing. Trials with the latest-generation LVADs have reported survival rates of 85% to 92% [1]. According to leading European and American societies, LVADs are an established therapy for end-stage HF [2, 3]. However, LVAD-related complications are still common and include pump thrombosis, HF worsening (HFW), right ventricular failure (RV-HF), drive-line infections (DRI), stroke, and bleeding.

Polish data on LVADs are scarce [4]. Since 1988, more than 500 HTxs have been performed at the John Paul II Hospital in Krakow. In October 2015, an LVAD programme was initiated. The aim of this study is to report up-to-date data on LVADs, including survival rates and complications.

METHODS

This is a prospective, all-comers study of 32 consecutive patients who underwent LVAD implantation between November 2015 and October 2017. All data collected were based on

hospitalisation and outpatient records. The study was approved by the local Ethics Committee.

We created an end-stage HF team, which included cardio-surgeons (B.K. and K.W.), cardiologists, cardio-anaesthetists, and associated personnel. Upon discharge, patients and their families were informed about LVAD management and provided with a 24/7 telephone line.

The primary endpoint was composed of death and pump thrombosis. Secondary (safety) endpoints included: RV-HF, urgent hospitalisation due to HFW, DRI, and bleedings.

Statistical analysis

Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the primary endpoint, its individual component events, and secondary endpoints. Survival data were analysed using the Kaplan-Meier method and compared with the log-rank test. To examine the associations of selected variables with endpoints of interest (unadjusted analyses and analyses adjusted for age, INTERMACS score, and N-terminal pro-B-type natriuretic peptide [NT-proBNP] level) Cox proportional hazards models were used. All the analyses were conducted in R software,

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Table 1. Comparisons of primary and secondary endpoints in patients stratified according to heart failure (HF) aetiology, INTERMACS score, and time of left ventricular assist device implantation

| | DCM (n = 17) | ICM (n = 15) | INTERMACS 1–2 (n = 7) | INTERMACS > 3 (n = 25) | First 16 | Last 16 |
|------------------|-----------------|-----------------|--------------------------|---------------------------|----------|-------------------------|
| Primary endpoint | 5 (29.4) | 3 (20) | 1 (14.3) | 7 (28) | 7 (43.7) | 1 (6.2) |
| HR, 95% CI | 1 | 0.6 (0.12–3.1) | 1 | 2.3 (0.24–23) | 1* | 0.086 (0.009–0.81)* |
| Death | 3 (17.6) | 1 (6.7) | 1 (14.3) | 3 (12) | 3 (18.7) | 1 (6.2) |
| HR, 95% CI | 1 | 0.3 (0.03–3.6) | 1 | 0.82 (0.07–9.3) | 1 | 0.29 (0.03–3.13) |
| Pump thrombosis | 2 (11.8) | 2 (13.3) | 0 (0) | 4 (16) | 4 (25) | 0 (0) |
| HR, 95% CI | 1 | 1.15 (0.14–9.4) | 1 | > 1000 (< 0.01–> 100) | 1* | < 0.001 (< 0.01–> 100)* |
| RV failure | 5 (29.4) | 4 (26.7) | 2 (28.6) | 7 (28) | 7 (43.7) | 2 (12.5) |
| HR, 95% CI | 1 | 0.87 (0.19–4.1) | 1 | 0.97 (0.15–6.2) | 1* | 0.18 (0.03–0.95)* |
| HF worsening | 6 (35.3) | 6 (40) | 1 (14.3) | 11 (44) | 9 (56) | 3 (18.7) |
| HR, 95% CI | 1 | 1.2 (0.29–5.1) | 1 | 4.7 (0.5–45.2) | 1* | 0.18 (0.04–0.9)* |
| Bleedings | 3 (17.6) | 5 (33.3) | 1 (14.3) | 7 (28) | 5 (31.2) | 3 (18.7) |
| HR, 95% CI | 1 | 2.3 (0.45–12.1) | 1 | 2.3 (0.24–23.04) | 1 | 0.51 (0.1–2.62) |
| Infections | 5 (29.4) | 6 (40) | 3 (42.8) | 8 (32) | 5 (31.2) | 6 (37.5) |
| HR, 95% CI | 1 | 1.6 (0.4–6.9) | 1 | 0.63 (0.1–3.5) | 1 | 1.3 (0.3–5.7) |

Data are shown as number (percentage); CI — confidence interval; DCM — dilated cardiomyopathy; HR — hazard ratio; ICM — ischaemic cardiomyopathy; RV — right ventricular; p-values for comparison between subgroups: *p < 0.05

version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). All results were considered statistically significant when p was < 0.05.

RESULTS AND DISCUSSION

The baseline characteristics of the study population, divided according to HF aetiology into ischaemic (n = 15) and dilated cardiomyopathy (DCM, n = 17), showed that men constituted the majority (94%) (**Suppl. Table 1 — see journal website**). New York Heart Association class (ischaemic HF: 4 ± 0.3 vs. DCM: 3.8 ± 0.4 ; p = NS) and INTERMACS scores (2.8 ± 0.4 vs. 2.7 ± 0.7 ; p = NS) were similar. The left ventricular (LV) cavity was larger in the DCM group (79.3 ± 13.1 mm vs. 71.7 ± 6.5 mm; p < 0.05), but the ejection fraction was comparable ($13.3\% \pm 3.8\%$ vs. $13.8\% \pm 3.4\%$; p = NS). NT-proBNP levels were significantly higher in the DCM group (8960 ± 10108 pg/mL vs. 3323 ± 2294 pg/mL; p < 0.05).

During the observational period of 12.2 ± 7.3 months, primary endpoint occurred in eight (24%) patients; death was reported in four (12%), and pump thrombosis in four (12%). Endpoints were analysed in all patients and subdivided into three categories: (1) according to HF aetiology: ischaemic vs. non-ischaemic, (2) INTERMACS score 1–2 vs. 3, and (3) first 16 vs. last 16 patients (Table 1). Patients stratified according to HF aetiology or INTERMACS were similar in terms of the of the primary endpoint. However, primary endpoint was more common in the first half compared to the second half of the population (7 [43.7%] vs. 1 [6.2%]; HR 0.086; 95% CI 0.009–0.81; p < 0.05). With regard to

the primary endpoint components, numbers of deaths were comparable between the groups (3 [18.7%] vs. 1 [6.2%]; HR 0.29; 95% CI 0.03–3.13; p = NS), whereas pump thrombosis was more frequent in the first half compared to the second half of patients (4 [25%] vs. 0 [0%]; p < 0.05). None of the following variables were predictors of the primary endpoint: LVAD type, prior cardiac arrest, chronic kidney disease (CKD), atrial fibrillation, patent foramen ovale (PFO), or the levels of haemoglobin, creatinine, urea, creatine kinase (CK), CK-MB, D-dimer, troponin, and C-reactive protein.

Right ventricular failure was observed in nine (27.3%) patients and was similarly distributed in patients grouped according to HF aetiology and INTERMACS. However, RV-HF was more common in the first 16 LVAD recipients (7 [43.7%] vs. 2 [12.5%]; HR 0.18; 95% CI 0.03–0.95; p < 0.05). PFO was the only independent predictor of RV-HF in a model adjusted for age, INTERMACS score and NT-proBNP level (HR 35.8; 95% CI 1.33–969.8; p < 0.05).

Hospitalisation due to HFW occurred in 12 (40%) patients. HFW was more common in the first half of the population (9 [56%] vs. 3 [18.7%]; p < 0.05). Only CKD was an independent predictor of HFW in an adjusted model (HR 1.86; 95% CI 1.08–3.96; p < 0.05).

Drive-line infections and bleeding complications occurred in 11 (34%) and eight (24%) patients, respectively. The frequencies of both complications were similar in all three patient subgroups.

The LVAD registries report similar baseline characteristics of the device recipients, and the frequency of ischaemic HF

and DCM is almost 50/50. Recent years have seen a shift towards implanting less seriously ill patients (INTERMACS 3–5) as compared to the historical pattern of LVAD implantations in morbid/dying patients (INTERMACS 1–2) [5].

In the early LVAD trial, REMATCH (1998–2001), one-year survival estimates were 52% in the LVAD compared to 25% in the medical group [6]. According to the INTERMACS registry (2008–2014), one- and two-year survival of 12,030 LVAD patients was 80% and 70%, respectively [1, 5]. In the recent MOMENTUM 3 (2014–2015) trial 13 (8.5%) out of 152 HeartMate3 and 14 (9.8%) out of 142 HeartMateII patients died within six months [7]. Our results are concordant with the published reports. Furthermore, we observed a striking 91.4% relative risk reduction in the primary endpoint in the 16 patients implanted later.

In the early days, pump thrombosis was reported in almost 20% of patients but has been reduced to the current incidence of 10% to 12%. We reported the occurrence of pump thrombosis in four (12%) patients, which is comparable to the current rates.

Left ventricular assist device supports the systemic ventricle; thus, RV function is crucial for recovery. The frequency of RV-HF after LVAD implantation is reported at 35% [8]. Surprisingly, we observed, for the first time, that RV-HF was independently associated with the presence of PFO. The mechanisms of this association are unknown. We speculate that during the progression of LV dysfunction, an increase in left atrial pressure could have resulted in the PFO opening, leading to an interatrial shunt. An increase in RV volume may have an additional damaging effect on RV morphology and function.

Apart from the difficulties of continuous anticoagulation with vitamin K antagonists, over time LVAD recipients develop acquired von Willebrand disease. At the same time, many patients develop arteriovenous malformations in the mucosa of the gastrointestinal tract. Taken together, LVAD patients are predisposed to bleedings. In the early REMATCH trial, the frequency of bleeding was 42% [8]. Clinically relevant bleeding, which is a typical complication, occurred in eight (24%) patients from our cohort.

Patients with LVADs are particularly predisposed to DRI. The typical site of infection is the exit site of the driveline. DRIs were reported in 17 (12%) and sepsis in 16 (11.4%) patients out of 140 subjects from the INTERMACS registry [1, 5].

In conclusion, a long-term LVAD programme is feasible in the Polish medical system; however, it requires a highly-specialised cardiac centre. The safety profile is comparable to that in experienced Western centres. Over 91% risk reduction in the latter half of patients supports a learning curve and accumulation of experience. Newly-found associations between PFO and RV-HF need further exploration.

Conflict of interest: none declared

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